In the claims:

Please cancel claims 11, 12, 27 and 28.

In claims 4 and 25, please delete "consist" and insert --consists-- therefor.

In claims 6 and 26, please insert --second-- between "co-administered" and "cells".

In claim 10, please insert --second-- between "said" and "cells".

C1

3. (Twice Amended) A method of treating a disease in a mammal wherein said method comprises co-administering of retinal pigmented epithelial (RPE) cells with a second cell population to the mammal, wherein said co-administered second cells [that] supply a therapeutic protein or other biologically active molecule, wherein said RPE cells and said co-administered second cells [that supply a therapeutic protein or other biologically active molecule] are allogeneic [or xenogeneic] to the mammal and wherein said RPE cells are administered in an amount effective to create an immunologically privileged site and said co-administered second cells [that supply a therapeutic protein or other biologically active molecule] are administered in an amount effective to sustain a therapeutic effect.

C2

5. (Amended) The method of Claim 3 wherein said co-administered second cells [that produce said therapeutic molecule] are cells transformed by a nucleic acid encoding said therapeutic protein or other biologically active molecule.

C3

15. (Twice Amended) The method of Claim 3 wherein the RPE cells, or co-administered second cells, [that supply the therapeutic protein or other biologically active molecule] are re-administered in an effective amount to sustain a therapeutic effect.

16. (Twice Amended) A pharmaceutical composition comprising retinal pigmented epithelial (RPE) cells and a second cell population, wherein the second cells [that]

produce a therapeutic protein or other biologically active molecule, wherein said RPE cells are allogeneic [or xenogeneic] to the second cells [that produce the therapeutic protein or other biologically active molecule], and a pharmaceutically acceptable carrier.

18. (Twice Amended) A pharmaceutical composition comprising retinal pigmented epithelial (RPE) cells and a second cell population, wherein the second cells [that] produce a therapeutic protein[,] or other biologically active molecule, wherein said RPE cells and the second cells are attached to a matrix[,] and wherein said RPE cells are allogeneic [or xenogeneic] to the second cells [that produce the therapeutic protein, or other biologically active molecule].

19. (Twice Amended) The composition of Claim 16 [or 18] wherein said therapeutic protein[,] or other biologically active molecule consists of a growth factor, cytokine, hormone, peptide fragment of a hormone, inhibitor of cytokines, differentiation factor or neurotransmitter.

21. (Amended) A compartmentalized kit adapted to receive a first container adapted to contain retinal pigmented epithelial (RPE) cells and a second container adapted to contain a second cell population, wherein said RPE cells are allogeneic to the second cells and wherein the second cells [that] produce a therapeutic molecule that is absent or defective in a disease.

22. (Amended) A compartmentalized kit adapted to receive a first container adapted to contain retinal pigmented epithelial (RPE) cells and a second container adapted to contain pancreatic islet of Langerhans cells, wherein said RPE cells are allogeneic to the pancreatic islet of Langerhans cells.

23. (Twice Amended) An article of manufacture comprising a packaging material, retinal pigmented epithelial (RPE) cells contained within said packaging material, a second cell population contained within said packaging material, wherein the second cells [that] produce a therapeutic protein or other biologically active molecule [contained within said packaging material and RPE cells contained within said packaging material], wherein said RPE cells are allogeneic [or xenogeneic] to the second cells [that produce the therapeutic protein or other biologically active molecule], wherein said RPE cells are effective for creating an immunologically privileged site in a mammal, and wherein said packaging material contains a label that indicates that said RPE cells can be used for creating an immunologically privileged site in a mammal.

C5

Please add the following claims:

30. (New) The method according to claim 13 wherein the disease consists of a neurological disease.

C6

31. (New) The method of claim 3 wherein the RPE cells and the co-administered second cells are re-administered in an effective amount to sustain a therapeutic effect and wherein the RPE cells and the co-administered second cells are attached to a matrix prior to re-administration.

32. (New) The composition of claim 18 wherein said therapeutic protein or other biologically active molecule consists of a growth factor, cytokine, hormone, peptide fragment of a hormone, inhibitor of cytokines, differentiation factor or neurotransmitter.

II. REMARKS

Claims 3-16, 18, 19 and 21-32 are pending in this application and claims 3-16, 18, 19, 21-23 and 25-32 are under consideration. Claims 3-16, 18, 19, 21-23 and 25-29 were rejected

under 35 U.S.C. §112, first paragraph. Claims 3-7, 9-16 and 19 were rejected under 35 U.S.C. §112, second paragraph. Claims 3, 4, 7, 9, 12, 13, 16, 19, 25, 28 and 29 were rejected under 35 U.S.C. §102(b). Claims 3, 4, 6, 7, 9, 10, 12, 13, 16, 18, 19, 21, 23, 25, 26, 28 and 29 were rejected under 35 U.S.C. §102(e). Claims 3, 5, 7, 8, 11, 14 and 15 were variously rejected under 35 U.S.C. §103(a).

By virtue of this response, claims 11, 12, 27 and 28 have been cancelled, claims 30, 31 and 32 have been added and claims 3, 4, 5, 6, 10, 15, 16, 18, 21, 22, 23, 25 and 26 have been amended to more clearly define the invention. Accordingly, claims 3-10, 13-16, 18, 19, 21-23, 25, 26 and 29-32 are currently under consideration.

Support for the amendments to the claims and for the new claims is found throughout the specification. Support for the amendment to claims 3, 16, 18 and 23 is found, *inter alia*, on page 4, lines 16-20 and page 6, line 35 to page 7, line 2. Support for the amendment to claims 21 and 22 is found, *inter alia*, on page 7, lines 26-31. Support for new claim 31 is found, *inter alia*, on page 16, lines 1-6. Support for new claim 32 is found, *inter alia*, in claim 4 as originally filed.

Thus, the amendments to the claims do not constitute new matter. The amendments and cancellation of certain claims were made solely to promote prosecution and without prejudice or disclaimer of any previously claimed subject matter.

Applicants have carefully considered the points raised in the official action and believe the Examiner's concerns can be addressed as described herein, thereby placing this case in condition for allowance.

Rejection under 35 U.S.C. §112, first paragraph

Claims 3-16, 18, 19, 21-23 and 25-29 were rejected under 35 U.S.C. §112, first paragraph for allegedly not being enabled for the invention as claimed. Applicants respectfully traverse this rejection.

The Examiner's concerns are essentially related to the effective "scope" of the enablement. The Examiner admits that the specification is "enabling for allogeneic

transplantation for at least 8 months" but finds that the specification "does not reasonably provide enablement for any transplantation in any animal for any sustained period" (Final Office Action, page 2).

In order to expedite prosecution of the instant application, the amended claims are now directed to RPE cells, and use thereof, in an allogeneic context. However, Applicants maintain that the question regarding the use of RPE cells for xenogeneic transplantation does not undermine enablement and reserve the right to pursue claims regarding the use of RPE cells in a xenogeneic context in related applications.

The Examiner states that Ye teaches "that transplantation of allogeneic tissue were rejected by at least 8 months" (Final Office Action, page 4, emphasis added). In Ye, however, the transplanted cells were examined at 8 months after transplantation. The transplanted RPE cells were found to be "readily and reliably identified on the recipient Bruch's membrane eight months after transplantation" (Ye abstract, page 629). In addition, the transplanted RPE cells in Ye were found in "close contact with host photoreceptors" and found to "form junctional complexes with neighboring RPE cells" (see, for example, page 637, first column, and Figure 6). Thus, Ye does not teach that allogeneic RPE transplants are rejected by at least 8 months.

In sum, Applicants' specification provides a presumptively sufficient disclosure. It teaches each and every element of the claimed invention, namely methods to treat a disease in a mammal wherein retinal pigmented epithelial (RPE) cells are co-administered with a second cell population. The RPE cells and the co-administered second cells are allogeneic to the recipient mammal. The second cell population supplies a therapeutic protein or other biologically active molecule and the RPE cells are administered in an amount effective to create an immune privileged site.

Applicants respectfully request that the Examiner reconsider and withdraw the rejections under 35 U.S.C. §112, first paragraph.

Rejection under 35 U.S.C. §112, second paragraph

Claims 3-7, 9-16 and 19 were rejected under 35 U.S.C. §112, second paragraph for allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

Although Applicants believe that the claims were sufficiently definite in view of the understanding of those of skill in the art, Claim 3 has been amended in order to enhance clarity and to facilitate disposition of the present case.

With regard to the rejection of claims 4, 9, 25 and 29 for the use of allegedly improper Markush groups, Applicants respectfully traverse these rejections.

In the rejection of these claims, the Examiner asserts that claims 4 and 9 contain allegedly improper Markush groups "because growth factors and cytokines can be inhibitors of other cytokines. Growth factors are hormones or peptide fragments of hormones. Cytokines and growth factors are hormones or peptide fragment of hormones. Cytokines and growth factors cause differentiation in stem cells. Growth factors can be neurotransmitters." Likewise, the Examiner asserts that claims 25 and 29 contain allegedly improper Markush groups by pointing out that a "chemokine may be an interleukin, interferon or CSF. An angiogenic factor may be an interleukin, interferon or CSF." (See Final Office Action, pages 4 and 5).

The members recited in the Markush groups of these claims are well known molecules and means and methods to distinguish such molecules are well known to those skilled in the art.

The double inclusion of an element by members of a Markush group is not, in itself, sufficient basis for objection to or rejection of claims (M.P.E.P. §2173.05(h)). Court decisions have held that there is no *per se* rule of indefiniteness concerning overlapping members where alternatives are recited in a claim, *e.g.*, members of a Markush group. See, for example, *in re* Kelly, 305 F.2nd 909, 134 U.S.P.Q. 397 (CCPA 1962), M.P.E.P. §2173.05(o). The mere fact that a compound may be embraced by more than one member of a Markush group recited in the claim does not lead to any uncertainty as to the scope of that claim for examination or infringement purposes. (M.P.E.P. §2173.05(o)).

In the statements above, the Examiner has inferred that some compounds of one group may also be embraced by another group recited in the claim. However, the Examiner has not provided any further support for the rejection of these claims.

Applicants believe that these claims are sufficiently definite in view of the understanding of those skilled in the art.

Applicants respectfully request reconsideration and withdrawal of the rejections under 35 U.S.C. §112, second paragraph.

Rejection under 35 U.S.C. §102(b)

Claims 3, 4, 7, 9, 12, 13, 16, 19, 25, 28 and 29 were rejected under 35 U.S.C. §102(b) as allegedly being anticipated by Ye (1993, *Current Eye Research*, 12:629-639). Applicants respectfully traverse this rejection.

The claimed invention is directed to methods for treating a disease in a mammal by co-administering RPE cells with a second cell population, wherein the RPE cells and the co-administered second cells are allogeneic to the mammal. The co-administered second cell population supplies a therapeutic protein or other biologically active molecule. The RPE cells are administered in an amount effective to create an immunologically privileged site and the second cells are co-administered in an amount effective to sustain a therapeutic effect. Other pending claims are directed to compositions comprising RPE cells and a second cell population. The second cell population supplies a therapeutic protein or other biologically active molecule.

Ye describes transplantation of allogeneic RPE cells to the retina of rabbits. Ye does not teach co-administration of RPE cells with a second cell population, much less co-administration of RPE cells with a second cell population, wherein the second cells supply a therapeutic protein or other biologically active molecule. Thus, Ye does not teach the claimed invention and, accordingly, Ye does not effectively anticipate the present invention.

Applicants respectfully request reconsideration and withdrawal of the rejections under 35 U.S.C. §102(b).

Rejection under 35 U.S.C. §102(e)

Claims 3, 4, 6, 7, 9, 10, 12, 13, 16, 18, 19, 21, 23, 25, 26, 28 and 29 were rejected under 35 U.S.C. §102(e) as allegedly being anticipated by Cherksey (U.S. Patent 5,618,531). Applicants respectfully traverse this rejection.

As described above, the present invention is directed to methods for treating a disease in a mammal by co-administering an effective amount of RPE cells to create an immunologically privileged site and an effective amount of a second cell population to supply a therapeutic protein or other biologically active molecule. In the claimed methods, the RPE cells and the co-administered second cells are allogeneic to the mammal. Pending claims are also directed to compositions comprising RPE cells and a second cell population, wherein the second cell population produces a therapeutic protein or other biologically active molecule. In the claimed compositions, the RPE cells are allogeneic to the second cell population.

Cherksey describes neural or paraneural cells, including RPE cells, attached to a matrix and administered to the brain for the treatment of Parkinson's Disease. Cherksey also describes "co-culture of neural or paraneural cells with glial cells, their co-incubation with a support matrix, followed by implantation of the support matrix carrying both cell types" (column 9, lines 3-6).

Cherksey does not teach or suggest that the glial cells co-incubated and implanted with neural or paraneural cells are allogeneic relative to the animal recipient and/or relative to the neural or paraneural cells. Thus, Cherksey does not teach the claimed invention.

The Examiner also states that Cherksey teaches the "glial cells are a glioma cell line and allogeneic to the animal (column 8, lines 59-60)" (Final Office Action, page 6). Cherksey does not teach that glial cells are glioma cells. This citation in Cherksey describes the co-culturing of adrenal medullary cells with glioma cells *in vitro* and does not teach that these glioma cells were implanted into an animal.

Also, the grafted glial cells described by Cherksey in column 8, line 65 to column 9, line 2 from Doering et al. (1984, *J. Neurol. Sci.* 63:183-196) refers to transplants of glial cells alone into brains of syngeneic mice.

For a claim to be anticipated by a reference, that reference must disclose each and every element of the claim. Cherksey does not teach the claimed invention. Accordingly, Cherksey does not effectively anticipate the present invention.

Applicants respectfully request reconsideration and withdrawal of the rejections under 35 U.S.C. §102(e).

Rejection under 35 U.S.C. §103

Claims 3, 14 and 15 were rejected under 35 U.S.C. §103 as allegedly being unpatentable over Cherksey. Claims 3, 5, 7, 8 and 11 were rejected as allegedly being unpatentable over Cherksey in view of Goldstein (U.S. Patent 5,300,436). Applicants traverse these rejections.

Applicants respectfully point out that the cited references do not support *prima facie* obviousness with regard to the claimed invention.

The claimed invention is directed to methods for treating a disease in a mammal by co-administering RPE cells with a second cell population, wherein the RPE cells and the co-administered second cells are allogeneic to the mammal. The co-administered second cell population supplies a therapeutic protein or other biologically active molecule. The RPE cells are administered in an amount effective to create an immunologically privileged site and the second cells are co-administered in an amount effective to sustain a therapeutic effect.

Cherksey teaches administration of matrix-attached neural or paraneural cells, including RPE cells, to the brain or spinal cord. Cherksey also describes implantation of a support matrix carrying both glial cells and neural or paraneural cells. However, contrary to the Examiner's statements in the paragraph bridging pages 7 and 8 of the Final Office Action, Cherksey does not teach that these glial cells are allogeneic with regard to the neural or paraneural cells or with